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Trend analysis of thyroid carcinoma incidence: A retrospective analysis of 2,705 cases from an endemic goiter region

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Abstract

Aim: To provide further data from a population with different genetic background for the contrary views on the ensuing question of "whether iodine status influence the onset and course of thyroid cancer" by examining trends in thyroid cancer incidence and prevalence of main sub types of thyroid cancer in a population from formerly iodine deficient geographic area in Türkiye.

Materials and Methods: Data were retrieved for 2,705 patients (2,161 female, 544 male) who were diagnosed with histopathologically confirmed thyroid cancer at Karadeniz Technical University Farabi Hospital, a university hospital serving a geographic region which remains an endemic goiter area and was formerly iodine-deficient, shortly after mandatory national salt iodization, between 2000 and 2018. Age, gender, subtype, tumor size, stage, and the changes and trends over the years were retrospectively evaluated.

Results: Thyroid cancer rates had a trend of increase from 2000 to 2012 and then began to decline. In our region, papillary thyroid cancer (PTC) is more prevalent (93.5%). Among all thyroid cancers, the ratio of micro papillary thyroid cancer (mPTC) is 46.5%, follicular thyroid cancer (FTC) is only 3.5%. mPTC (tumor size ≤10 mm) (49.8%) and macroPTC (tumor size >10 mm) (50.2%) are approximately equal in proportion, and these ratios remained similar over the years covered in this analysis. Stage I PTC is 95.3%. M0 PTC is 98.9%.

Conclusion: Data from this retrospective epidemiologic study indicates that the rate of PTC is notably high and thyroid cancer may have a more benign course in our endemic goiter region probably due to iodine supplementation that may affect late-stage thyroid carcinogenesis.

Introduction

Thyroid cancer is the most common cancer of the endocrine system, characterized by low mortality and morbidity but has an increasing incidence trend. According to the GLOBOCAN data published in 2018, which included 185 countries, the incidence of thyroid cancer was ranked 11th among all cancers, with a rate of 3.1%, while the mortality rate was 0.4% [1]. According to the GLOBOCAN 2022 data, thyroid cancer was ranked 7th with an incidence rate of 4.1%, with the mortality rate of 0.5% [2]. Over the last 30 years, the global incidence of thyroid cancer has significantly increased, primarily due to the rise in papillary thyroid cancer (PTC) [3]. In Turkey, thyroid cancer is the second most common cancer among women and ranks 8th among men [4].

Differentiated thyroid cancer (DTC), which includes papillary and follicular subtypes, constitutes the vast majority (>90%) of all thyroid cancers [5]. Most thyroid cancers are PTC, followed by follicular thyroid cancer (FTC) [6,7].

FTC constitutes 5 to 50% of differentiated thyroid cancers. Its relative incidence tends to increase in iodine-deficient endemic regions [8]. FTC is more common in areas with iodine deficiency. However, the increasing incidence of PTC is thought to be due to changing diagnostic criteria and dietary iodine supplementation-induced decrease in the frequency of FTC cases [9].

The ratio of PTC to FTC differs in regions according to the risk factors including the status of iodine, adequate and deficient iodine levels, delayed impacts of iodine deficiency, and intense screening. In iodine-deficient areas, lower rates are reported. In many parts of the world, dietary iodine supplementation have caused an increase in

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the ratio of PTC to FTC [10]. Consequently, the combined effects of changes in diagnostic criteria and iodine supplementation may have played a significant role in the reported decreasing trend in FTC incidence over time. It has also noted that FTC has a higher incidence in some regions of the world with iodine deficiency, compared to other areas [11,12]. Populations that have begun iodine prophylaxis show an increase in the ratio of PTC to FTC [13].

Studies on this subject present current data from different regions of the world, but they do not clearly identify the reasons for the increasing trend. The most widely accepted explanation is the overdiagnosis of microcancers, particularly due to the use of advanced diagnostic techniques and increased screening. To provide an additional perspective on this issue, we took an opportunity to conduct a new analysis of cases at our university hospital where most of the goiter cases of an endemic goiter region receive treatment. Furthermore, our previous analysis (covering 2006-2008 period) from this region had revealed rate of 26.5% confirming endemic goiter status of this region [14].

The World Health Organization (WHO) defines iodine deficiency as a median urinary iodine excretion of less than 100 µg/L in children aged 6 years and older, and adults. Adequate iodine intake is defined as a urinary iodine excretion of 100-199 µg/L [15]. In 1997, two studies identified our region of Trabzon as an iodine-deficient area; the median urinary iodine excretions in 11-year-old children were found to be 13 µg/L [16], and the average iodine excretion was 31.3 µg/L [17]. However, in a study we conducted in 2008, the median urinary iodine excretions in adults were found to be 122.79 µg/L, indicating adequate iodine intake.

Our region is also an endemic goiter region. Endemic goiter is defined as the condition where thyroid enlargement (goiter) exceeds 10% of the population in a given area [18]. In a study we conducted in 2008, the prevalence of goiter in adults in the Trabzon region was found to be 26.5% [14].

To determine iodine deficiency, measuring urinary iodine concentration is the most practical biochemical method. This approach assesses impact of iodine supplementation only at the time of measurement, whereas thyroid size reflects the impacts of iodine nutrition over months or years, delayed impact. Therefore, even if populations have achieved iodine sufficiency based on average urinary iodine concentration, goiter may persist [15]. In Turkey, to reduce iodine deficiency, it has been mandated by legislation that iodine be added to salt (50–70 mg/kg potassium iodide or 25–40 mg/kg potassium iodate) since 1999.

It has been reported that with the normalization of iodine deficiency in endemic goiter regions, the epidemiological profile of thyroid cancer is subject to change, with an increase in thyroid cancer incidence. This provides significantly improved prognosis due to opportunity of early-stage diagnosis [19]. The same study reported that with the normalization of iodine deficiency, the incidence of anaplastic thyroid cancer (ATC) decreased, the incidence of PTC significantly increased (from 56% to 91.5%), and the stages of thyroid cancer improved.

The available epidemiological and experimental evidence suggest that iodine deficiency is a risk factor for TC and this can be ameliorated by iodine intake. However, though less convincing, there are also evidence suggesting that iodine excess may actually be associated with increased incidence of TC. To provide further evidence for this ensuing question we took opportunity of re-analyzing our data from a formerly iodine deficient region of Turkey, in correspondence to initiation of national iodine supplementation. Our data does not only provide data from a different genetic background but also offer a relatively large population from a formerly iodine deficient still endemic region to trace over about 20-years.

In this study, we have found that in an endemic goiter region, formerly identified with iodine deficiency, the increase in thyroid cancer at halt and even tended to decline. The occurrence rate of mPTC (micro papillary thyroid cancer, tumor size ≤10 mm) and MPTC (macro papillary thyroid cancer, tumor size >10 mm) were approximately equal over the years. Additionally, the data from our study showed that thyroid cancer in endemic goiter regions is more benign (Stage 1 rates: 95.3% in PTC, 81.1% in FTC, and 34.2% in MTC).

Materials and Methods

Study population

The protocol of this study was approval by the Karadeniz Technical University Medical Faculty/Trabzon Ethics Committee (25/06/2018, no:154).

This study included 2,705 patients (2,161 female, 544 male) whose thyroid cancer diagnose was histopathologically confirmed at the Karadeniz Technical University Medical Faculty, a tertiary care center and university hospital. All the cases diagnosed with of thyroid cancer between 1 January 2000 and 30 June 2018, were considered for this retrospective evaluation.

Inclusion criteria involved cases to have a pathologically confirmed diagnosis of TC and being over 18 years of age. All information about the patients included in the study was obtained from the hospital's electronic archive: the patients' age, gender, diagnosis dates, radiological imaging reports and histopathological data after thyroidectomy. Patients with sufficient clinical details (thyroid cancer subtype) specified in the International Statistical Classification of Diseases and Related Health Problems (ICD) code in the data archive were identified and evaluated on a case-by-case basis by our study team.

Thyroid cancer is classified into seven diagnostic groups according to the WHO 2017 criteria: PTC, FTC, medullary thyroid carcinoma (MTC), Hurthle cell carcinoma (HCC), ATC, poorly differentiated carcinoma, and mixed type thyroid carcinoma (MTTC) [20]. For PTC, tumor size was categorized as ≤10 mm (microcarcinoma, mPTC) and >10 mm (macrocarcinoma, MPTC).

FTC was divided into two subtypes: minimally invasive and widely invasive.

The thyroid cancer cases were evaluated for tumor size, vascular invasion, lymph node metastases, and distant organ metastasis. Staging was based on the criteria of the American Joint Committee on Cancer (AJCC). Since the

AJCC 8th edition was published [21] during the data analysis, this staging was performed by the research team using the data from the patient files.

Statistical analysis

For the analysis of the data, the SPSS 23.0 statistical software package (SPSS Inc., Chicago, IL, USA) was used. Descriptive statistics of the evaluation results were presented as numbers and percentages for categorical variables, and as mean, standard deviation, minimum and maximum for numerical variables. Comparisons of numerical variables between two independent groups were evaluated using the Mann-Whitney U test. The Chi-square test was used to analyze the differences in the ratios of categorical variables between independent groups. A p value <0.05 was considered statistically significant.

Results

Of the 2,705 cases included in the analysis, 79.9% (n=2161/2705) were female and 20.1% (n=544/2,705) were male. The rate of thyroid cancer was significantly higher in females compared to males (p<0.001). Female cases were observed four times more often. The overall average age at diagnosis was 48.4±12.7 (47.7±12.8 for females, 51.3±11.9 for males). The average age of female was significantly lower when compared to male (p<0.001).

Among all thyroid cancers: PTC constituted 93.5% (n=2,530/2,705), FTC 3.5% (n=95/2,705), MTC 1.7% (n=45/2,705), ATC 0.6% (n=16/2,705), HCC 0.3% (n=7/2,705), MTTC 0.4% (n=11/2,705), and poorly differentiated carcinoma 0.03% (n=1/2,705) (Table 1). Poorly differentiated carcinoma was not included in the tables as there was only one case.

When PTC was evaluated; mPTC (tm size ≤1cm) was 49.8% (1,260/2,530) and MPTC (tm size >10 mm) was 50.2% (1,270/2,530) with approximately equal rates (Table 1).

When evaluating the diagnosis dates of thyroid cancers, it was observed that the highest number of diagnoses occurred in 2012. The most frequent diagnosis year for females was 2013, while for males it was 2012. It was found that the number of cancer cases started to decrease after 2013 in females and after 2012 in males (Figure 1).

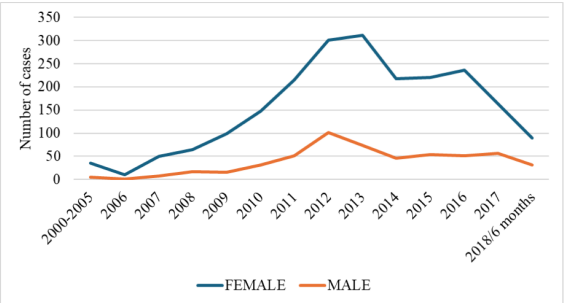

Figure 1. Distribution of overall thyroid cancers stratified by gender over the study period.

Table 1. General characteristics and types of thyroid cancer cases.

	Overall (n=2705)		Female (n=2161/79.9%)		Male (n=544/20.1%)		p value <0.001*
Age (years)¥	48 (39-57)		47 (39-57)		52 (43-60)		<0.001+
Thyroid Cancer type	n	%	n	%	n	%	
PTC	2530	93.5	2040	94.4	490	90.1	
microPTC (≤10mm)	1260	49.8	1045	51.2	215	43.9	
macroPTC (>10 mm)	1270	50.2	995	48.8	275	56.1	
FTC	95	3.5	70	3.2	25	4.6	
MTC	45	1.7	26	1.2	19	3.5	
ATC	16	0.6	10	0.5	6	1.1	
HCC	7	0.3	6	0.3	1	0.2	
MTTC	11	0.4	8	0.4	3	0.6	
Total	2705	100	2161	100	544	100	

PTC: Papillary Thyroid Cancer, mPTC: Micro papillary Thyroid Cancer, MPTC: Macro papillary Thyroid Cancer, FTC: Follicular Thyroid Cancer, MTC: Medullary Thyroid Cancer, ATC: Anaplastic Thyroid Carcinoma, HCC: Hurthle Cell Carcinoma, MTTC: Mixed Type Thyroid Cancer, ¥Median (IQR), +Mann-Whitney U test, p<0.05, *Chi-square test; p<0.05.

Cancer cases with pathologically determined tumor size and those with imaging methods performed for staging were classified and staged according to the TNM classification (Differentiated and anaplastic thyroid carcinoma TNM staging, AJCC UICC 8th edition) [21] (Table 2).

The highest rates according to tumor size were: 50.1% T1A in PTC, 44.4% T2 in FTC, 33.3% T4A in MTC, 60% T4A in ATC, 33.3% T2 and T3A in HCC, and 36.4% T1B in MTTC (Table 2).

The highest rates of lymph node involvement were: 93.0% N0 in PTC, 90.5% N0 in FTC, 56.1% N1B in MTC, 100% N1B in ATC, 71.4% N0 in HCC, and 81.8% N0 in MTTC (Table 2).

When cancers were evaluated according to metastases status, the presence of distant metastases (M1) was found to be: 1.1% in PTC, 8.0% in FTC, 22.0% in MTC, and 80.0% in ATC. No metastases were observed in HCC and MTTC (Table 2). The highest rate of distant organ metastases was seen in ATC (Table 2).

When evaluated according to stages, it was found that PTC was most frequent in Stage 1 (95.3%) and least frequent in Stage 4A (0.049%), FTC was most frequent in Stage 1 (81.1%) and least frequent in Stage 4A (1.2%), MTC was most frequent in Stage 1 (34.2%) and least frequent in Stage 4B (2.6%), ATC was most frequent in Stage 4C (80%) and least frequent in Stage 4A (20%), HCC was most frequent in Stages 1 and 2 (33.3%, 33.3%) and least frequent in Stages 3 and 4B (16.7%, 16.7%), and MTTC was most frequent in Stage 1 (90.9%) and least frequent in Stage 2 (9.1%) (Table 2).

When cancers were evaluated according to the diagnosis date, it was found that PTC was most frequently diagnosed in 2012 (15.3%), FTC in 2010 (23.2%), MTC in 2012

Table 2. TNM classification and stages of thyroid cancer types.

Tumor Size	PTC		FTC		MTC		ATC		HCC		MTTC	
	n	%	n	%	n	%	n	%	n	%	n	%
T1A	1257	50.1	5	6.2	7	19.4	0	0	1	16.7	2	18.2
T1B	681	27.1	16	19.8	5	13.9	0	0	0	0	4	36.4
T2	429	17.1	36	44.4	5	13.9	1	10	2	33.3	3	27.3
T3A	84	3.3	12	14.8	4	11.1	0	0	2	33.3	1	9.1
T3B	6	0.2	0	0	0	0	0	0	0	0	0	0
T4A	51	2.0	10	12.3	12	33.3	6	60	0	0	1	9.1
T4B	3	0.1	2	2.5	3	8.3	3	30	1	16.7	0	0
TOTAL	2511	100	81	100	36	100	10	100	6	100	11	100
Lymph Node Involvement												
N0	2299	93.0	76	90.5	18	43.9	0	0	5	71.4	9	81.8
N1A	61	2.5	2	2.4	0	0	0	0	1	14.3	1	9.1
N1B	110	4.5	6	7.1	23	56.1	10	100	1	14.3	1	9.1
TOTAL	2470	100	84	100	41	100	10	100	7	100	11	100
Metastases												
M0	2439	98.9	80	92.0	32	78.0	3	20	7	100	11	100
M1	27	1.1	7	8.0	9	22.0	12	80	0	0	0	0
TOTAL	2466	100	87	100	41	100	15	100	7	100	11	100
Stage												
STAGE 1	2348	95.3	69	81.1	13	34.2	0	0	2	33.3	10	90.9
STAGE 2	82	3.3	10	11.8	6	15.8	0	0	2	33.3	1	9.1
STAGE 3	19	0.8	3	3.5	5	5.3	0	0	1	16.7	0	0
STAGE 4A	1	0.0	1	1.2	11	28.9	3	20	0	0	0	0
STAGE 4B	15	0.6	2	2.4	1	2.6	0	0	1	16.7	0	0
STAGE 4C^{+}	-	-	-	-	5	13.2	12	80	-	-	-	-
TOTAL	2465	100	85	100	38	100	15	100	6	100	11	100

PTC: Papillary Thyroid Cancer, mPTC: Micro PTC, MPTC: Macro PTC, FTC: Follicular Thyroid Cancer, MTC: Medullary Thyroid Cancer, ATC: Anaplastic Thyroid Carcinoma, HCC: Hurthle Cell Carcinoma, MTTC: Mixed Type Thyroid Cancer, $^{+}$ for MTC/ATC.

(15.6%), ATC in 2010 and 2011 (25% and 25%), HCC in 2009 and 2017 (28.6% and 28.6%), and mixed type thyroid cancer in 2010 (27.3%) (Table 3). When all TCs were evaluated, the year with the most diagnoses were found to be 2012.

When the most common cancer type, PTC, was evaluated as mPTC and MPTC according to diagnosis dates, it was found that both mPTC and MPTC were most frequently diagnosed in 2012. The trend graph also showed an increase over the years, but a decrease was observed after 2012 (Table 4, Figure 2).

When comparing PTC and FTC by diagnosis years, it was observed that PTC showed an increasing trend until 2012, after which it began to decrease, while the number of FTC occurrence remained unchanged over the study period (Figure 3).

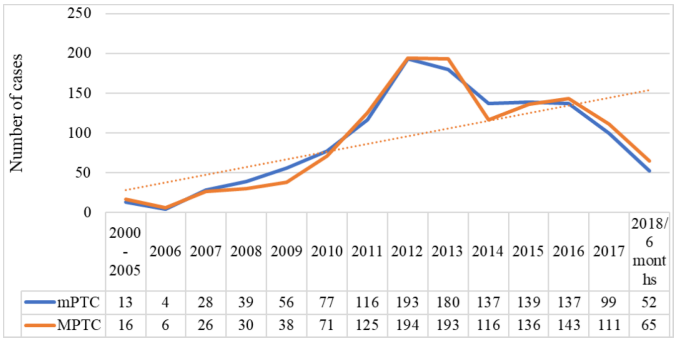

Figure 2. Micro papillary thyroid cancer and macro papillary thyroid cancer over the study period (2000-2018).

Discussion

Incidence of TC, the most common endocrine malignancy, especially PTC has continued to increase worldwide in recent years. The reason for this rise is not fully understood. Although the contribution of an increasing amount of screening to diagnosis is acknowledged [22,23], it cannot fully explain the rising trend of these cases. Lifestyle, obesity, environmental factors, or complications are considered potential risk factors for TC [24]. Among these factors, iodine status is very critical since this trace mineral is vital for thyroid function. Thus, implementation of iodine supplementation is widely applied in iodine deficient areas but PTC consequences of these policies have been debated for many years, with experimental and epidemiological studies reporting conflicting results [24,25]. To contribute to clarification of this discussion, we obtained data through the analysis of relatively large numbers obtained over a long period from the Trabzon region (for-

Table 3. Date of diagnosis in our cohort with regard to thyroid cancer sub-types.

Diagnosis date	PTC		FTC		MTC		ATC		HCC		MTTC	
	n	%	n	%	n	%	n	%	n	%	n	%
2000-2005	29	1.1	7	7.3	3	6.7	0	0	0	0	0	0
2006	10	0.4	1	1.1	0	0	0	0	0	0	0	0
2007	54	2.1	3	3.2	0	0	1	6.3	0	0	0	0
2008	69	2.7	9	9.5	3	6.7	0	0	0	0	0	0
2009	94	3.7	13	13.7	3	6.7	1	6.3	2	28.6	1	9.1
2010	148	5.8	22	23.2	3	6.7	4	25.0	0	0	3	27.3
2011	241	9.6	16	16.8	4	8.9	4	25.0	1	14.3	0	0
2012	387	15.3	8	8.4	7	15.6	0	0	0	0	1	9.1
2013	373	14.7	4	4.2	5	11.1	1	6.3	1	14.3	2	18.2
2014	253	10.0	5	5.2	3	6.7	2	12.5	0	0	1	9.1
2015	265	10.5	4	4.2	3	6.7	1	6.3	0	0	1	9.1
2016	280	11.1	1	1.1	5	11.1	1	6.3	0	0	0	0
2017	210	8.3	2	2.1	6	13.3	0	0	2	28.6	1	9.1
2018*	117	4.6	0	0	0	0	1	6.3	1	14.3	1	9.1
TOTAL	2530	100	95	100	45	100	16	100	7	100	11	100

PTC: Papillary Thyroid Cancer, FTC: Follicular Thyroid Cancer, MTC: Medullary Thyroid Cancer, ATC: Anaplastic Thyroid Carcinoma, HCC: Hurthle Cell Carcinoma, MTTC: Mixed Type Thyroid Cancer, *first 6 months.

Table 4. Micro papillary thyroid cancer and macro papillary thyroid cancer over the study period (2000-2018).

Diagnosis years	mPTC		MPTC	
	n	%	n	%
2000-2005	13	1.0	16	1.3
2006	4	0.3	6	0.5
2007	28	2.2	26	2.0
2008	39	3.1	30	2.4
2009	56	4.4	38	3.0
2010	77	6.1	71	5.6
2011	116	9.2	125	9.8
2012	193	15.3	194	15.3
2013	180	14.3	193	15.2
2014	137	10.9	116	9.1
2015	139	10.2	136	10.7
2016	137	10.9	143	11.3
2017	99	7.9	111	8.7
2018/6 months	52	4.1	65	5.1
TOTAL	1260	100	1270	100

mPTC: Micro Papillary Thyroid Cancer, MPTC: Macro Papillary Thyroid Cancer.

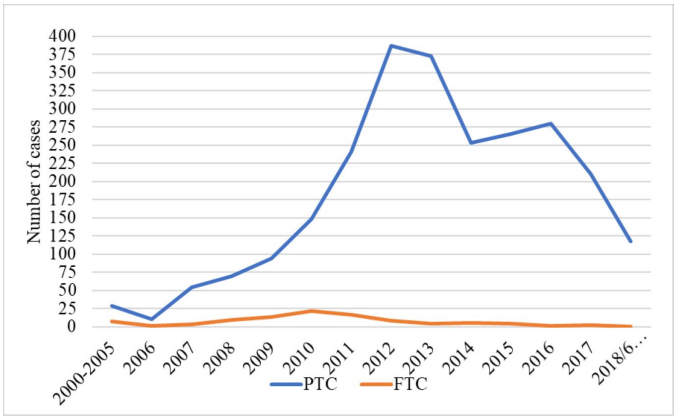

Figure 3. Trends in thyroid cancer subtypes (PTC and FTC) cases during 2000–2018.

merly iodine-deficient, currently an endemic goiter region) and found that iodine supplementation may reduce the overall prevalence of TC, particularly PTC. And our analysis also revealed that following iodine supplementation, with a certain delay, there has been a significant reduction in aggressiveness of TC indicating a benign course.

This retrospective analysis on identifying the types, trends, and changes over the years of thyroid cancer in our endemic goiter region previously deficient in iodine, found that thyroid cancer cases were on steady rise from the start of our analysis at 2000 until 2012 and then began to decrease. We have to note that nationwide iodine supplementation was started in 1999. Among the cases PTC was more common with 93.5%, and the rate of mPTC among all TCs was found to be 46.5%. The occurrence rate of FTC was only 3.5%. mPTC (49.8%) and MPTC (50.2%) were observed in approximately equal proportions. Stage I PTC was 93.5%. M1 PTC was only 1.1%.

Due to chronic TSH overstimulation there is a close relation between thyroid tumors and iodine deficiency, and this has been subject to many investigations particularly iodine deficient areas. Grebe et al. reported in their study that the relative rate of FTC tends to increase in iodine-deficient regions [8]. Grani et al. stated that the ratios of PTC to FTC differ in regions with sufficient and deficient iodine, with FTC being more prevalent in iodine-deficient regions, and that iodine supplementation in the diet has increased the ratio of PTC to FTC in many parts of the world [10]. FTC has also been reported to be more common in iodine-deficient Africa [26]. In Turkey, iodine began to be added to salt in 1999. Our study covers the years

2000-2018. Despite our study region being an endemic goiter area, PTC increased over the years, but there was no significant change in the rate of FTC. PTC was significantly higher from 2000 to 2012 and began to decrease in 2012. In our study, the rate of FTC remained the same from 2000 and began to increase from 2007, then started to decrease after 2010.

Approximately 90% of all thyroid cancers are reported to be differentiated thyroid cancer (PTC+FTC) [5,6]. In our study, the rate of PTC+FTC was found to be 97% (93.5% papillary and 3.5% follicular), which is higher than the rates reported in the literature. When evaluating the stages of papillary cancer, data from the USA National Cancer Institute (covering the years 2014-2020) showed that 64% were localized, 30% had regional spread, 3% had metastases, and 3% were of unknown stage [27]. According to AJCC 2018, Stage I and II cancers constitute the majority of PTCs, while Stage III and IV cancers make up less than 10% [9]. In our study, according to AJCC 2018, Stage I and II PTC accounted for 98.6% (95.3% and 3.3%, respectively). Stage III and IV only made up 1.4% (0.8% and 0.6%, respectively). In our endemic goiter region, almost all PTC cases were found to be at Stage I, indicating that they were detected at a much earlier stage compared to the literature. We believe that this may be due to the endemic goiter region or the easier access to healthcare services in Turkey, especially to endocrinology clinics, and the high usage of ultrasonography, leading to overdiagnosis.

In a study conducted in an endemic goiter region with iodine replacement, the follicular cancer subtype was found to be 61.4% minimally invasive and 38.6% widely invasive [28]. In our study, these rates were higher for the minimally invasive subtype and lower for the widely invasive subtype (80% and 20%, respectively). In our endemic goiter region, follicular cancer appears to have a more benign course. Although we do not have a clear explanation for this, their longer period of follow up might account for this difference. In a study published in 2013 by Hyeyeun Lim et al. investigating the status of thyroid cancer in United States of America (USA), the proportion of female among all thyroid cancer cases was found to be 75.3%, while the proportion of male was 24.7% [29]. In a study by Pizzato and colleagues, as well as in the GLOBOCAN 2022 data, thyroid cancer was found to be three times more common in women than in men [2,30]. In a study conducted in Iran (between 2009and 2018), 1,742 thyroid cancer cases were recorded (83.7% in female and 16.3% in male). The incidence of thyroid cancer was found to be 5.1 times higher in women than in men [31]. In a study conducted in Zurich, Switzerland, covering the years 1980-2016, it was reported that thyroid cancer was 27.7% in men and 72.3% in women [32] In a study from Turkey by Özdemir and colleagues, which included 8,450 thyroid cancer cases, the proportion of women was reported to be 79.1% and men 20.9% [33]. In our study, the proportion of thyroid cancer in women was found to be 79.9% and in men 20.1%, and thyroid cancer was found to be four times more common in women than in men. The rate of thyroid cancer in women in our study was within similar range compared to international literature and at comparable levels reported by a study conducted in western city of Izmir, Turkey [33].

In the USA, the largest increase in thyroid cancer occurred between 1992 and 2009, with a significant decrease in the increasing trend beginning between 2009 and 2014. After 2014, the incidence of thyroid cancer began to stabilize [22]. In an endemic goiter region in India, a study covering the years 2008-2015 reported a marked increase in mPTC [34]. Many studies have indicated that thyroid cancer is overdiagnosed, particularly due to inclusion of microcancers [6,30,35,36]. In a narrative review published in 2015 by Riccardo Vigneri et al., it was reported that in the last 20 years, the incidence of thyroid cancers has increased more than any other cancer, and this increase was especially noted in mPTCs [37]. The greatest increase was related to small-sized tumors (microcarcinomas), which rose to nearly 50% among all tumors. In a study published in 2021 by Adalberto Miranda et al., it was noted that the rapid increase in thyroid cancer incidence from 1998 to 2012 was observed only in papillary thyroid cancer, primarily due to its subclinical forms [38]. In a study from Turkey by Özdemir M. and colleagues, mPTC was found to be 24.2% [33], while in our study, mPTC was found to be 49.8%, which is similar to international literature but higher than national literature. In our study, the situation specifically indicating an excessive number of mPTC cases was not observed. mPTC and MPTC showed similar rates of increase and decrease over the years. While the same study emphasized a continuous increase in thyroid cancer over the years, our study found an increase in all types of thyroid cancer until 2012, after which it began to decrease. We believe that the decrease in cancer incidence after 2012 is due to more nodules being monitored with close follow-up, and biopsies being performed only on high-risk nodules, a decrease in biopsy rates, and consequently, a decrease in surgeries.

When evaluating thyroid cancer types, Bakiri et al. reported that FTC and ATC were more common in endemic regions (42.1% and 14%, respectively) compared to non-endemic regions (38.4% and 6.2%, respectively) [39]. In a 2003 publication by Susan Preston-Martin et al. (analyzing studies covering the years 1980-1997), the rates were 79% PTC, 14% FTC, 2% MTC, 1% ATC, 1% other histopathologies, and 3% unknown histopathological type [35] . In a study by Hyeyeun Lim et al. published in 2013, which included 77,276 thyroid cancer cases from 1974 to 2013, the rates were found to be 83.6% PTC, 10.8% FTC, 2.2% MTC, 1.3% ATC, and 2.1% others [29]. In a study conducted in an endemic goiter region in India, the rates were 97% PTC, 0.6% FTC, and 2.4% MTC [34]. In Iran, a study by Maryam Ghalandari et al. reported rates of 86.8% PTC, 3.7% FTC, 1.8% MTC, 0.5% ATC, and 7.2% others [31]. In a study covering the years 1980-2016 in Switzerland, the rates were found to be 65.8% PTC, 23.4% FTC, 5.2% ATC, 3.1% MTC, and 2.5% others [32]. According to the 2018 cancer statistics from the Turkish Ministry of Health Public Health Directorate, the rates were 94.3% PTC, 3.6% FTC, 1.6% MTC, and 0.5% other cancers [4]. In a study from Turkey by Özdemir and colleagues covering the years 1992-2017, the reported rates were 91.2% PTC, 5.7% FTC, 2.3% MTC, and 0.7% ATC. In our study, the rates were found to be 93.5% PTC, 3.5%

FTC, 1.7% MTC, 0.6% ATC, and 0.7% others (0.3% HCC, 0.4% mixed type, and 0.03% poorly differentiated carcinoma) [33]. In our study, the rate of PTC was higher compared to international literature but similar to studies conducted in Turkey.

Limitations of our study include its retrospective nature and the fact that the subtypes of PTC were not specified confirmed in the pathological reports of for all the patients involved in the analysis. We believe this is due to pathologists often not specifying subtypes in mPTC cases. The rate of unspecified subtypes in the entire cohort is 40%. The rate of unspecified subtypes in mPTC is 38.5%, while in PTC (>10 mm), it is only 11.4%. We consider this to be within acceptable limits. Additionally, some patients' radiological imaging reports, which could have been used to evaluate lymph node metastasis and distant metastasis, were not accessible. The rate of these inaccessible radiological reports in the entire cohort is 10%. We also consider this to be within acceptable limits compared to retrospective nature of this study. Registry data did not include information on other relevant risk factors that may vary regionally, including socioeconomic status, obesity, diet, radiation exposure, and family history, limiting the assessment of alternative risk factors. And, this analysis was performed on data from a single institution. However, this also have some advantages considering the opportunity of analyzing data from a formerly iodine deficient endemic area.

In our study, the exact duration of iodine supplementation for the participating patients is not known precisely. However, national iodine supplementation began in Turkey in 1999. It is logical to attribute the breakpoint occurring after 2012, which contrasts with the increasing trend in thyroid cancers close to the onset of the national intervention, to the long-term effects of the supplementation initiated in 1999. Although there is not exact data on the time of delay of impact of iodine supplementation on the trend of thyroid cancer incidence, available data present similar latency with our study. Thus, a recent study from China shows deceleration in the number of TC cases at 2016 following implementation of a nationwide salt iodization programme in 1996 [40]. So, it is likely that delayed effects of iodine supplementation peaks about 10-years' time frame.

Conclusion

Overall, this retrospective analysis clearly shows that during the study period, although the incidence rates of thyroid cancers increased steadily, cases tends to have more benign course. Although this study did not address any cause-effect impact, this is probably due to the delayed/long-term effects of iodine supplementation.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Ethical approval

This study protocol was reviewed and approved by the Ethics Committees of Karadeniz Technical University Medical Faculty/Trabzon; approval number: 154-25/06/2018.

Disclosure

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